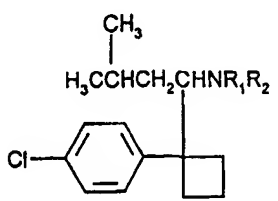




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/135	A1	(11) International Publication Number: WO 00/56313 (43) International Publication Date: 28 September 2000 (28.09.00)
<p>(21) International Application Number: PCT/US00/07130</p> <p>(22) International Filing Date: 17 March 2000 (17.03.00)</p> <p>(30) Priority Data: 60/125,340 19 March 1999 (19.03.99) US</p> <p>(71) Applicant: KNOLL PHARMACEUTICAL COMPANY [-/US]; 3000 Continental Drive-North, Mount Olive, NJ 07828-1234 (US).</p> <p>(72) Inventors: MENDEL, Carl, M.; 8 Great Hills Terrace, Short Hills, NJ 07078 (US). SEATON, Timothy, B.; 192 Liberty Corner Road, Far Hills, NJ 07931 (US). WEINSTEIN, Steve, P.; 22 Dunham Road, Hartsdale, NY 10530 (US).</p> <p>(74) Agent: MAURER, Barbara, V.; BASF Corporation, 3000 Continental Drive-North, Mount Olive, NJ 07828-1234 (US).</p>	<p>(81) Designated States: AT, AU, BG, BR, CA, CN, CZ, DE, DK, ES, FI, GB, HR, HU, ID, IL, IN, IS, JP, KR, LT, LU, LV, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, TR, UA, ZA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: METHOD OF CONTROLLING WEIGHT GAIN ASSOCIATED WITH THERAPEUTIC DRUGS</p> <div style="text-align: center;">  <p>(I)</p> </div> <p>(57) Abstract</p> <p>A compound of formula (I), or a pharmaceutically acceptable salt thereof in which R₁ and R₂ are independently H or methyl (for example <i>N,N</i>-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl amine hydrochloride optionally in the form of its monohydrate) is used for treating weight gain associated with treatment with certain drug therapy, including the use of tricyclic antidepressants, lithium, sulphonylureas, beta-adrenergic blockers, certain steroid contraceptives, corticosteroids, insulin, cyproheptadine, sodium valproate, neuroleptics, phenothiazine or piztifin.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

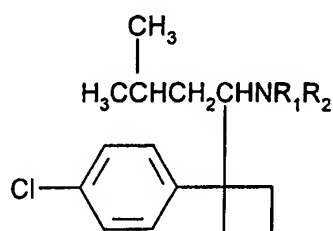
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Method of Controlling Weight Gain Associated With Therapeutic Drugs

This invention relates to a method of controlling weight gain associated
5 with treatment with medicines.

According to the present invention there is provided a method of
controlling weight loss associated with treatment with certain therapeutic drugs, in
which a therapeutically effective amount of a compound of formula I

10



including enantiomers and pharmaceutically acceptable salts thereof, in which R₁
and R₂ are independently H or methyl, is administered in conjunction with a
15 pharmaceutically acceptable diluent or carrier to a human in need thereof.

The use of certain therapeutic drugs can promote weight gain. These
drugs include tricyclic antidepressants, lithium, sulphonylureas, beta-adrenergic
blockers, certain steroid contraceptives, corticosteroids, insulin, cyproheptadine,
20 sodium valproate, piztifin, neuroleptics including typical neuroleptics for example
phenothiazine and phenothiazine derivatives such as chlorpromazine,
thioridazine, fluphenazine and trifluoperazine; butyrophenones such as
haloperidol; thioxanthenes such as flupentixol and substituted benzamides such
as sulpiride, atypical neuroleptics including clozapine, olanzapine, zotepine,
25 risperidone, quetiapine and ziprasidone.

A preferred compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine or a salt thereof, for example the hydrochloride salt. A preferred form of this hydrochloride is its monohydrate.

5 The preparation and use of compounds of formula I, such as N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine, N-{1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutyl}-N-methylamine, and 1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine and salts thereof, in the treatment of depression is described in British Patent Specification 2098602 and US Patent
10 4,522,328. The use of compounds of formula I such as N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and salts thereof in the treatment of Parkinson's disease is described in published PCT application WO 88/06444. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and salts thereof in the treatment of cerebral function disorders is described in US
15 Patent 4,939,175. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in the treatment of obesity is described in published PCT application WO90/06110. A particularly preferred form of this compound is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate (sibutramine hydrochloride) which is described in
20 European Patent Number 230742. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and salts thereof for improving the glucose tolerance of humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus is described in published PCT application
WO95/20949.

25

It will be appreciated by those skilled in the art that compounds of formula I contain a chiral centre. When a compound of formula I contains a single chiral centre it may exist in two enantiomeric forms. The present invention includes the use of the individual enantiomers and mixtures of the enantiomers. The
30 enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which may be

separated, for example, by crystallisation; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by
5 separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further
10 step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

15 Preferred compounds of formula I are N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine, N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-methylamine, and 1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine including racemates, individual enantiomers and mixtures thereof, and pharmaceutically acceptable salts thereof.

20 The individual enantiomers can be prepared by enantioselective synthesis from optically active precursors, or by resolving the racemic compound which can be prepared as described above. Enantiomers of secondary amines of the formula I can also be prepared by preparing the racemate of the corresponding
25 primary amine, resolving the latter into the individual enantiomers, and then converting the optically pure primary amine enantiomer into the required secondary amine by methods described in British Patent Specification 2098602.

Specific examples of compounds of formula I are:

30

(+)-N-[1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl]-N-methylamine;

- (-)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-methylamine;
(+)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;
(-)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;
(+)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine;
5 (-)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine.

The hydrochloride salts are preferred in each case, but the free bases and other pharmaceutically acceptable salts are also suitable.

- 10 The compound of formula I may be administered in any of the known pharmaceutical dosage forms. The amount of the compound to be administered will depend on a number of factors including the age of the patient, the severity of the condition and the past medical history of the patient and always lies within the sound discretion of the administering physician but it is generally envisaged that
15 the dosage of the compound to be administered will be in the range 0.1 to 50 mg preferably 1 to 30 mg per day given in one or more doses.

- Oral dosage forms are the preferred compositions for use in the present invention and these are the known pharmaceutical forms for such administration,
20 for example tablets, capsules, granules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared from a mixture of the active compound with fillers, for example calcium phosphate; disintegrating agents, for example maize starch; lubricating agents, for example magnesium
25 stearate; binders, for example microcrystalline cellulose or polyvinylpyrrolidone and other optional ingredients known in the art to permit tableting the mixture by known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethylcellulose phthalate. The tablets may be formulated in a
30 manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided

with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods and, if desired, provided with enteric coatings in a known manner. The contents of the capsule may be formulated using known methods so as to give sustained release of the active compound. The tablets and capsules may conveniently each contain 1 to 50 mg of the active compound.

Other dosage forms for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil. The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example, water) before ingestion. The granules may contain disintegrants, eg an effervescent couple formed from an acid and a carbonate or bicarbonate salt to facilitate dispersion in the liquid medium.

The therapeutically active compounds of formula I may be formulated into a composition which the patient retains in his mouth so that the active compound is administered through the mucosa of the mouth.

Dosage forms suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

Dosage forms suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Dosage forms for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared
5 by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, e.g. paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream, gel or ointment base. The amount of active
10 compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The therapeutically active compound of formula I may be formulated into
15 a composition which is dispersed as an aerosol into the patients oral or nasal cavity. Such aerosols may be administered from a pump pack or from a pressurised pack containing a volatile propellant.

The therapeutically active compounds of formula I used in the method of
20 the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as an oily
25 suspension of the compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or a lipophilic ester or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing
30 part of the compound to be delivered. The amount of active compound present in

an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

5 In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

10 In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

15 The invention further provides the use of compounds of formula I in the manufacture of a medicament for controlling weight gain in a patient treated with certain therapeutic drugs which are known to cause weight gain.

20 In another aspect, the invention further provides a pharmaceutical composition for preventing weight gain in a patient treated with tricyclic antidepressants, lithium, sulphonylureas, beta-adrenergic blockers, certain steroid contraceptives, corticosteroids, insulin, cyproheptadine, sodium valproate, neuroleptics, phenothiazine and piztifin, comprising a compound of formula I in conjunction with a pharmaceutically acceptable diluent or carrier.

25 Monoamine reuptake inhibitors have been used to treat certain of the disorders described in the present invention. However, these compounds are known to suffer from a number of disadvantages. Firstly such compounds are not effective in all patients. Secondly where the compounds are effective they may not provide a complete cure of the disorder. Thirdly, there are many undesirable side-effects known with this type of compound. Such side-effects include nausea, sexual dysfunction, light headedness, somnolence, sweating,
30 tremor, dry mouth, asthenia, insomnia, diarrhoea, headache, vomiting, anxiety,

drowsiness, dizziness, fever, rash or allergic reactions, arthralgia, myalgia, convulsions, hypomania and mania.

Sibutramine (Formula I, $R_1 = \text{CH}_3$, $R_2 = \text{CH}_3$) has a pharmacological profile which is unique amongst monoamine reuptake inhibitors. Through its pharmacologically active metabolites, (metabolite 1, $R_1 = \text{H}$, $R_2 = \text{CH}_3$ in Formula I and metabolite 2, $R_1 = \text{H}$, $R_2 = \text{H}$ in Formula I) sibutramine inhibits the reuptake of all three monoamines differentiating it from serotonin (5-HT)-selective reuptake inhibitors, e.g. fluoxetine, noradrenaline-selective reuptake inhibitors, e.g. desipramine, dopamine-selective reuptake inhibitors, e.g. bupropion, and serotonin-noradrenaline reuptake inhibitors, e.g. venlafaxine (Table 1). It is this unique combination of pharmacological actions which renders sibutramine, and the other compounds of formula I, efficacious in control of weight gain associated with certain therapeutic drugs which are known to cause weight gain.

15

The assays below are performed in a similar manner to those described in WO98/41528.

TABLE

Comparison of the *in vitro* monoamine reuptake inhibition profiles of Examples 1
 5 and 2, and various reference monoamine reuptake inhibitors in rat brain tissue

	Ki (nM)		
	[³ H]Noradenaline	[³ H]5-HT	[³ H]Dopamine
Example 1	3	18	24
Example 2	5	26	31
Bupropion	2590	18312	409
Desipramine	2	200	4853
Fluoxetine	320	11	2025
Venlafaxine	196	26	2594

The results are the means of ≥ 3 separate determinations

Example 1 $R_1 = H$, $R_2 = CH_3$ in Formula I

10 Example 2 $R_1 = H$, $R_2 = H$ in Formula I

The efficacy of the compounds of formula I in treating weight gain associated with certain drug therapy is demonstrated by the following test.

15 Experiments were performed in individually-housed female Sprague-Dawley rats with free access to food (powdered rat chow containing 20% lard) and tap water at all times. On the day of the experiment, animals (n=10) were dosed orally with vehicle; the neuroleptic clozapine 3 mg/kg; sibutramine 3 mg/kg or sibutramine plus clozapine 3 mg/kg; and their food intake was monitored over 2 h. Clozapine

3 mg/kg produced a significant increase in food intake compared to the vehicle-treated control group (table 1). Sibutramine 3 mg/kg po significantly decreased food intake compared to the controls. Co-administration of sibutramine prevented the increase in food intake induced by clozapine. Indeed, animals given both sibutramine and clozapine ate similar amounts of food to the rats given sibutramine alone (table 1). These results demonstrate that sibutramine prevents the hyperphagia induced by clozapine in rats and indicate that sibutramine will be efficacious in controlling the weight gain associated with neuroleptics in the clinic.

10

Table 1 Sibutramine prevents clozapine-induced hyperphagia in rats

Treatment	Mean food intake (g/kg) \pm SEM
Vehicle	6.5 \pm 0.9
Clozapine 3 mg/kg	9.3 \pm 0.7 *
Sibutramine 3 mg/kg	1.7 \pm 0.6 **
Clozapine 3 mg/kg plus sibutramine 3 mg/kg	2.1 \pm 0.5 ** †

Significant differences from the vehicle-treated control group are denoted by * P < 0.01, ** P < 0.001. Significant antagonism of clozapine-induced hyperphagia is denoted by † P < 0.001 (Dunnett's test; two-tailed).

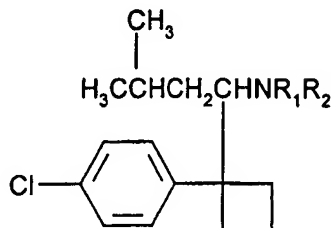
20

The efficacy of compounds of formula I in treating weight gain associated with certain drug therapy is also demonstrable through clinical trials in a relevant population set.

The invention has been described with reference to various specific embodiments. However, many variations and modifications may be made while remaining within the scope and spirit of the invention.

Claims

1. A method of treating weight gain associated with certain drug therapy comprising administering to a human in need thereof a therapeutically effective
5 amount of a compound of formula I



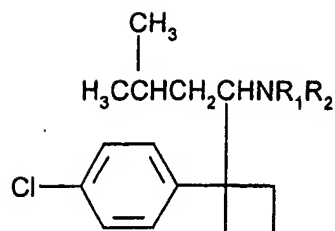
- including enantiomers and pharmaceutically acceptable salts thereof in which R₁ and R₂ are independently H or methyl, in conjunction with a pharmaceutically
10 acceptable diluent or carrier.

2. A method as claimed in claim 1 in which the drug therapy is treatment with tricyclic antidepressants, lithium, sulphonylureas, beta-adrenergic blockers, steroid contraceptives, corticosteroids, insulin, cyproheptadine, sodium valproate,
15 piztifin, neuroleptics including typical neuroleptics for example phenothiazine and phenothiazine derivatives such as chlorpromazine, thioridazine, fluphenazine and trifluoperazine; butyrophenones such as haloperidol; thioxanthenes such as flupentixol and substituted benzamides such as sulpiride, atypical neuroleptics including clozapine, olanzapine, zotepine, risperidone, quetiapine and
20 ziprasidone.

3. A method as claimed in claim 1 or 2 wherein the compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride.

- 25 4. A method as claimed in claim 1 or 2 wherein the compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in the form of its monohydrate.

5. A method as claimed in claim 1 or 2 wherein the compound of formula 1 is (+)-N-[1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl]-N-methylamine.
- 5 6. A method as claimed in claim 1 or 2 wherein the compound of formula 1 is (-)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-methylamine.
7. A method as claimed in claim 1 or 2 wherein the compound of formula 1 is (+)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine.
- 10 8. A method as claimed in claim 1 or 2 wherein the compound of formula 1 is (-)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine.
- 9 A method as claimed in claim 1 or 2 wherein the compound of formula 1 is
15 (+)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine.
10. The method as claimed in claim 1 or 2 wherein the compound of formula I is
(-)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine.
- 20 11. The method as claimed in claim 1 or 2 wherein the compound of formula I is (±)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-methylamine.
12. The method as claimed in claim 1 or 2 wherein the compound of formula I
25 is (±)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine.
13. The method as claimed in claim 1 or 2 wherein the compound of formula I is (±)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine.
- 30 14. The use of a compound of formula I



including enantiomers and pharmaceutically acceptable salts thereof in which R_1 and R_2 are independently H or methyl, in the manufacture of a medicament for treating weight gain associated with certain drug therapy.

5

15. The use as claimed in claim 14 in which the drug therapy is treatment with tricyclic antidepressants, lithium, sulphonylureas, beta-adrenergic blockers, certain steroid contraceptives, corticosteroids, insulin, cyproheptadine, sodium valproate, neuroleptics, phenothiazine or piztifin.

10

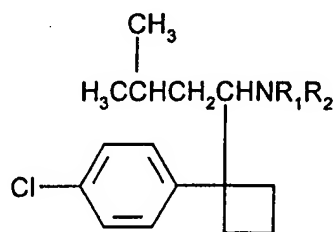
16. The use as claimed in claim 14 or 15 in which the compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride.

15

17. The use as claimed in claim 14 or 15 in which the compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate.

18. A pharmaceutical composition for treating weight gain associated with certain drug therapy, comprising a therapeutically effective amount of a compound of formula I

20



including enantiomers and pharmaceutically acceptable salts thereof in which R_1 and R_2 are independently H or methyl, in conjunction with a pharmaceutically acceptable diluent or carrier.

5 19. A pharmaceutical composition as claimed in claim 18 in which the compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride.

20. A pharmaceutical composition as claimed in claim 18 in which the
10 compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/07130**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) :A61K 31/135

US CL :514/646

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/646

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A - X	US 4,939,175 A (UKAI ET AL) 03 July 1990 (3/7/90), see entire document, especially column 1, lines 50-65.	1-13 ---- 14-20
Y - X	US 5,436,272 A (SCHEINBAUM) 25 July 1995 (24/7/95), see entire document.	1-13 ---- 14-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

17 MAY 2000

Date of mailing of the international search report

29 JUN 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

Dorothea Lawrence for
FREDERICK KRASS

Telephone No. (703) 308-1235